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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,338	11/14/2000	Yoshiyuki Ueno	1110-0279P	3959

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,338	UENO, YOSHIYUKI	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2005 and 27 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10-13,17 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8, 10-13, 17-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed October 27, 2004 and January 5, 2005 in response to the Office action of July 27, 2004 and the interview of November 16, 2004 is acknowledged. Claims 14-16 have been cancelled. Claims 8, 10-13, 17 and 18 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 103

The rejection of claims 8, 10-13, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Nature of Medicine, 1997), Harada et al. (Hepatology 1997, see IDS) and Shirakawa et al. (U.S. Pat. No. 6,114,507) **is maintained** for reasons of record. The following references have been cited in the response to Applicants arguments. The references evidence the state of the art at the time the invention was made: Kuroki et al., (Virchows Archives 1996, cited in IDS March 16, 2001), Graham et al., European Journal of Gastroenterology and Hepatology 1998, Vol. 110, pages 553-557, filed with the reply of May 8, 2003) and Crawford J.M., Chapter 18 The liver and the biliary tract, in Robbins Pathologic Basis of Disease, 5th ed. 1994, W.B. Saunders Company, Philadelphia, PA).

Applicant argues that is was not known at the time of the invention whether it was more desirable to inhibit Fas-mediated apoptosis with a Fas antagonist or to induce apoptosis with a Fas agonist in PBC or bile duct disappearance syndrome. Applicant argues that apoptosis is desirable in "other-immune based pathologies" such as rheumatoid arthritis, transplant rejection MS, CF or diabetes and because it is desirable in other disease it would not have been known

whether inhibition of apoptosis is desirable in treating PBC. The Office disagrees with this line of argument. At the time the invention was made (see Graham et al., European Journal of Gastroenterology and Hepatology 1998, Vol. 110, pages 553-557, filed with the reply of May 8, 2003) it was known that the induction apoptosis in biliary epithelial cells was undesirable and resulted in PBC. It was known in the art that the initial injury in PBC is the caused by the destruction of portal bile ducts (see Kuroki et al., Virchows Archives 1996, IDS March 16, 2001). Epithelial cells of the bile duct express Fas antigen. The presence of Fas antigen on target cell membranes is required for the signaling of the apoptosis cascade (see Trapani J.A. International Review of Cytology, 1998, Vol. 182, pp. 111-192, see page 147 and figure 3). The Fas antigen is important in the death of biliary epithelial cells via the apoptotic pathway (see Kuroki et al., Virchows Archives 1996, IDS March 16, 2001). Based on what is generally known in the prior art the argument that it might be desirable to induce apoptosis using the Fas/Fas ligand with an agonist is not convincing since cell death in the biliary duct leads to disease. There are two mechanism for inducing apoptosis one is through the secretory mechanism involving Ca2+ dependent perforin mediated lyses which is CD8+ T cell response and the other is through the nonsecretory pathway which uses the Fas/Fas ligand interaction (see Trapani J.A. International Review of Cytology, 1998, Vol. 182, pp. 111-192, see page 147 and figure 3). Applicant argues that Harada et al. does not provide prediction as to mechanistic involvement of Fas/Fas ligand in PBC. Applicant argues the "the critical question of whether Fas antagonist or Fas agonist is necessary for treating PBC" is not addressed in the cited reference. This argument is not convincing, based on what is taught in Harada et al. and what is generally known in the art the ordinary artisan studying liver disease would have been fully

aware at the time the invention was made that treatments which increase apoptosis, for example by inducing Fas mediated lyses, would not be desirable. Increasing apoptosis would not be desirable because it was known that apoptosis leading to cell death in the bile duct epithelial cells leads to disease. Applicant then makes the point that the various animal models used in the cited references are not models for PBC caused by an immunological mechanism but are models for fulminate hepatitis which is typically caused by viral infection. Apoptosis mediated by Fas antigen has been demonstrated by injecting mice with an antibody to Fas (an agonist that induces Fas mediated apoptosis). The Kondo reference uses two models, in one model the 6C2 cells were injected into mice expressing the HbsAg antigen. The 6C2 cells have both apoptosis systems available the perforin/granzyme system and Fas/Fas ligand system. In *in vivo* assays inhibiting the Fas/FasL ligand system was sufficient to prevent hepatitis. (see Trapani J.A. International Review of Cytology, 1998, Vol. 182, pp. 111-192, for a review of both killing mechanisms). The models are not specifically drawn to treatments treating primary biliary cirrhosis or bile duct disappearance syndrome which is caused by an immunological mechanism. "The fact that Kondo et al. considered models for only a specific form of hepatitis, i.e. fulminate hepatitis caused by infectious agents, is an important distinction for consideration of the presently amended claims." (see response page 5). The Office disagrees with Applicants' assessment that the particular models do not provide insight into the immunological mechanism involved in PBC. Models are just that they are models. Models can never precisely emulate the natural progression of disease in an animal. It was known in the prior art that the injection of mice with an antibody directed to Fas causes the mice to die because of liver failure. Antibodies to Fas will not distinguish between Fas on hepatocytes and Fas on epithelial cells (bile duct

epithelial cells), therefore, the use of antibodies in an animal model system will not be able distinguish specific tissues because the prior art antibodies will bind wherever the antigen is located. The important point of the reference is that it clearly teaches activating Fas mediated apoptosis is not desirable. Applicants' argument regarding the animal models is not persuasive.

In response to Applicants arguments that the ordinary artisan would have known that there may be different triggers which lead to hepatitis (inflammation of the liver) the problem is that clinically and histologically the difference between an immuno based mechanism and a viral based mechanism (which also involved an immune reaction) are indistinguishable. Autoimmune hepatitis, which involves an immunologic mechanism, is a chronic hepatitis of unknown etiology, which has clinical features virtually indistinguishable from chronic viral hepatitis. Autoimmune hepatitis present the entire spectrum of chronic hepatitis, and patients usually responds to immunosuppression, indicating that an immune-based mechanism is involved in the process. Drug induced chronic hepatitis is also clinically indistinguishable from chronic viral hepatitis and from autoimmune hepatitis. Drug induced hepatitis can occur via (1) direct toxicity (2) hepatic conversion of a compound to an active toxin (3) via immune mechanism. Immune mechanism in drug induced hepatitis usually are triggered when a drug acts to convert a normal cellular protein into a target by the immune system (see Crawford J.M., Chapter 18 The liver and the biliary tract, in Robbins Pathologic Basis of Disease, 5th ed. 1994, W.B. Saunders Company, Philadelphia, PA). The general teaching in the prior art is that anything that causes the loss of hepatocytes and subsequent regeneration of the hepatocytes results in the formation of cirrhosis. The involvement of an immune based mechanism in the etiology of PBC was known the prior art (see Kuroki et al., 1996 and Crawford J.M 1994). The general knowledge at the time of the

invention indicated that primary sclerosing cholangitis had a suspected autoimmune involvement, the disease also has a high association with inflammatory bowl disease implicating that the same mechanism is involved in both disease processes.

Argument (1) that "pathologies having different etiologies might have different apoptotic mechanisms." The involvement of an immune based mechanism in the etiology of PBC was known the prior art (see Kuroki et al., 1996 and Crawford J.M 1994). The art in general at the time the invention was made recognized that there are two apoptotic mechanism available in the CD8+ one is the perforin/granzyme system and the other is the Fas/Fas ligand system (see Trapani J.A. International Review of Cytology, 1998, Vol. 182, pp. 111-192, for a review of both killing mechanisms) Kondo et al. recognized that the model system they applied was able to prevent hepatitis formation by using an anti-Fas ligand antibody in the mouse model. The reference teaches that in the *in vivo* system by preventing apoptosis in hepatocytes the mice did not develop hepatitis. It was known in the prior art that development of PBC is associated with apoptosis, Harada et al. teaches that the biliary epithelial cells in PBC undergo apoptosis in response to the Fas/Fas ligand (CD95/CD95 ligand) crosslinking. The reference indicated that the perforin/granzyme pathway was also involved with the bile duct epithelial cell loss in PBC, but this system was not as active (minor). The combined teaching of Harada et al. and Kondo et al. indicate that although there are two apoptotic mechanism available the in liver injury blocking only one the Fas/Fas ligand method is sufficient as a preventative. Based on what was known in the prior art that the biliary epithelial cells express Fas and that the Fas/Fas ligand system is involved in the PBC the ordinary artisan would have had a high expectation of success in treating a patient with an anti-Fas ligand antibody.

Argument (2) because "other immune based disorders involving Fas/Fas ligand, which one might think to be predictive of the mechanism involved with PBC and bile duct disappearance syndrome caused by an immunological mechanism, have been found to be responsive to treatment with a Fas agonist (a compound that induces apoptosis), i.e. the complete opposite to the claimed invention." This argument is not persuasive since it was already known in the prior art that the destruction of liver cells by any means leads to hepatic dysfunction. Therefore, the ordinary artisan versed in the art of liver injury would not have thought that treatment methods that increase apoptosis, cell death, would be desirable.

Argument (3) is that "the potential role of Fas/Fas ligand and the mechanism of pathology in different hepatic pathologies was highly controversial at the time of the invention" The argument that the art may have been controversial at the time the invention was made is not a persuasive. PBC is a chronic progressive liver disease that is characterized by the destruction of bile ducts. The statement by Graham et al. that something is unlikely to occur is opinion by the author and is based solely on the low level of expression of CD95/Fas on these cells. It must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600. The art here is not inconsistent with the rejection set forth by the Office, the rejection is based on the observation that Fas (CD95) is present on the epithelial cells of bile ducts and that the triggering of the Fas system leads to hepatic failure. The role of apoptosis in the bile duct epithelial cells was known at the time the invention was made and there are only two mechanism that can account for apoptotsis (1) the perforin/granzyme system which in the references was found play a minor role

and (2) the Fas/Fas ligand system which was found to play the major role. Evidence for the role of the Fas/Fas ligand system is made by the observation that the induction of Fas apoptosis leads to hepatic failure while the prevention of apoptosis through the administration of anti-Fas ligand antibody leads to the prevention of hepatic failure in the animal model.

The combined teaching of Harada et al. and Kondo et al. indicate that although there are two apoptotic mechanism available the in liver injury blocking only one the Fas/Fas ligand mechanism is sufficient to be preventative. Based on what was known in the prior art that the biliary epithelial cells express Fas and that the Fas/Fas ligand system is involved in the PBC the ordinary artisan would have had a high expectation of success in treating a patient with an anti-Fas ligand antibody. In combination with Shirakawa et al. which discloses a broad method of treating a systemic or topical pathological condition, caused by the abnormality of Fas/Fas ligand system. The treatment method involves administering an anti-Fas ligand antibody to a patient. Kondo et al. show that Fas mediated apaotosis is involved in PBC. Employing the method of Shirakawa et al. the administration of anti-Fas ligand antibody would treat systemically all Fas/Fas ligand interactions. The ordinary artisan would have been motivated to use the antibody for the treatment of PBC because apoptosis has been implicated in the disease. The ordainry artisan would have had a high expectation of success in administering the antibody to a patient as set out in Harada et al. The rejection is maintained for reasons of record.

The rejection of claims 8, 10-13, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Nature of Medicine, 1997) Harada et al. (Hepatology 1997, see IDS) and Shirakawa et al. (U.S. Pat. No. 6,114,507) as evidenced by Galle et al. (Journal of Experimental

Medicine, 1995), Dienes et al. (Virchows Archievs 1997) and Luo et al. (Journal of Viral Hepatitis, 1997) **is maintained** for reasons of record. The following references have been cited in the response to Applicants arguments. The references evidence the state of the art at the time the invention was made: Kuroki et al., (Virchows Archives 1996, cited in IDS March 16, 2001), Graham et al., European Journal of Gastroenterology and Hepatology 1998, Vol. 110, pages 553-557, filed with the reply of May 8, 2003) and Crawford J.M., Chapter 18 The liver and the biliary tract, in Robbins Pathologic Basis of Disease, 5th ed. 1994, W.B. Saunders Company, Philadelphia, PA).

The combination of references of Kondo et al., Harada et al. and Shirakawa et al. has been discussed above. The general teaching in the prior art is that anything that causes the loss of hepatocytes and subsequent regeneration of the hepatocytes results in the formation of cirrhosis. The involvement of an immune based mechanism in the etiology of PBC was known the prior art (see Kuroki et al., 1996 and Crawford J.M 1994). At the time the invention was made it was known in the art that the initial injury in PBC is caused by the destruction of portal bile ducts (see Kuroki et al., Virchows Archives 1996, IDS March 16, 2001). Epithelial cells of the bile duct express Fas antigen. The Fas antigen is important in the death of biliary epithelial cells via the apoptotic pathway (see Kuroki et al., Virchows Archives 1996, IDS March 16, 2001). Based on what is generally known in the prior art the argument that it might be desirable to induce apoptosis with an agonist (induce Fas mediated apoptosis) is not convincing since cell death of epithelial cells in the biliary duct leads to disease. There are only two mechanism for inducing apoptosis one is through the secretory mechanism involving Ca2+ dependent perforin

mediated lyses which is CD8+ T cell response and the other is through the nonsecretory pathway which uses the Fas/Fas ligand interaction.

The reference of Galle et al. was cited for the additioanl showing that anti-Fas antibodies rapidly induce apoptotic cell death in primary human hepatocytes (see discussion and figure 2). The results confirm the expression of Fas/CD95 in normal human liver at constitutive low expression levels (see discussion, page 1227, column 2, paragraph 2). The reference of Diens et al. was cited to indicate that in primary biliary cirrhosis the bile duct epithelial cells express Fas/CD95 (see abstract). The presence of Fas/CD95 in the epithelial cells in the disease is required if the antibody treatment with the anti-Fas ligand antibody is to have an effect in the bile ducts. The reference of Luo et al. was cited that in a viral infection the Fas expression is upregulated in the hepatocytes making them more susceptible to Fas ligand interaction.

Based on the totality of the references it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat primary biliary cirrhosis by disrupting the Fas/Fas ligand interaction that leads to apoptosis of the cells involved in primary biliary cirrhosis as taught by Harada et al.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 3/18/05